Investigating the intention of pregnancy among women living with HIV and its effect on the early development of their HIV exposed infants.

By

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(MYXCHI002)

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Mini-Dissertation

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PREAMBLE

Declaration

I **Chido Moyo** hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Signed by candidate

Date: 7 February 2020

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~"The will of God will never lead you where the grace of God cannot keep you"~

Abstract

Background:

The increase in access and coverage of ART, including through prevention of mother-to-child transmission (PMTCT) programmes in Africa, has resulted in the reduction of vertical transmission, which has led to >95% of infants born to women living with HIV (WLHIV) in South Africa being born HIV uninfected. Concerns have however been raised regarding the health and development of HIV exposed and uninfected (HEU) infants. WLHIV in South Africa are more likely to have an unintended pregnancy compared HIV negative women. Unintended pregnancies continue to be a challenge towards the on-going strides and achievement of PMTCT goals. There is however a paucity of data on the investigations in research for the effect of unplanned pregnancy and early child development in South Africa. This research study focused on early infant development health outcomes of HIV exposed but uninfected (HEU).The aim of the study was to investigate the association between the intention of pregnancy among pregnant WLHIV, and the subsequent early child development of their HEU infants in Gugulethu, South Africa.

Methods: This study used data from the "Long-term Adherence and Care Engagement" study (LACE; May 2017-Apr 2018), which provided long-term data from women who had initiated antiretroviral therapy (ART) during pregnancy. During pregnancy, the London Measure of Unplanned Pregnancy was used to assess pregnancy intentions. At 36-60 months postpartum, child development was assessed across six developmental domains using the Ages & Stages questionnaire (ASQ). Multivariate Linear regression models were used to examine the association between pregnancy intentions and subsequent child development, with results reported as regression coefficients (β) with 95% confidence intervals (CI).

Results: A total of 250 mother-infant pairs completed assessments and were included in analysis. At enrolment, the median age for the women was 28.3 years, and 38% were married and/or cohabiting. Overall, based on the women's responses 58% of pregnancies were categorised as unplanned. Upon analysis, no associations were observed between pregnancy intention and all early child development domains $p>0.05$. Overall, infants with evidence of early developmental delay that scored below threshold (ASQ-3) were 8% for the gross motor domain, 19% for fine motor, 4% for communication, 15% for problem solving, and 7% for personal social domain. Whilst for the social emotional domain (ASQ: SE-2), two percent of infants scored above threshold and hence, had evidence of early developmental delay.

Conclusions:

Among women initiating ART during pregnancy, we observed no significant association between pregnancy intention and the early child development of their HEU infants. The findings of this research accentuate the need for targeted strategies towards psychosocial issues, and educational interventions for WLHIV and, for informed fertility decisions. Furthermore, the need for exploration of interventions to encourage infant-parent attachment and interaction for development, as well as the impact of pregnancy intentions on parenting behaviours.

List of Abbreviations

ASQ - Ages and stages Questionnaire

AIDS- Acquired Immune Deficiency Syndrome

ART - Antiretroviral Therapy (triple drug)

ARV - Antiretroviral

CUMC-IRB - Columbia University Medical Center Institutional Review Board

HEU - HIV Exposed but Uninfected

HEI - HIV exposed but infected

HIV - Human Immunodeficiency Virus

HUU - HIV Unexposed and Uninfected

LACE- Long Adherence Care Engagement Study

IQR - Inter-Quartile Range

MCH-ART - Maternal-Child Health Antiretroviral Therapy study

MTCT - Mother-to-Child Transmission

MOU - Midwife Obstetric Unit

PMTCT - Prevention of Mother-to-Child Transmission

PMTCT-ART- Prevention of Mother-to-Child Transmission- Antiretroviral Therapy (triple drug)

PLHIV-People Living With HIV

UCT-HREC - University of Cape Town Faculty of Health Sciences Human Research Ethics Committee

WLWHIV- Women Living With HIV

Figure Caption sheet

Figure 1: Percentages of HEU infants with evidence of developmental delays.

Figure 2: Percentage of infants with evidence of developmental delay by category of mother's pregnancy intention

**In accordance with Author instructions for The Child and Maternal Journal*

Contents of Mini-Dissertation

PART A – Protocol for the proposed study: Investigating the intention of pregnancy among women living with HIV and its effect on the early development of their HIV exposed infants.

PART B – Structured literature review

PART C – Journal manuscript – In accordance with the instructions four authors for *The Maternal Child Health Journal.*

PART A: PROTOCOL

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Introduction

Background

HIV/AIDS is still a leading epidemic in Africa this is regardless of the clinical advancements for prevention and care, contributions of internal and external funding and strides towards policy development (Dwyer-Lindgren et al., 2019; World Health Organization, 2018). Approximately 80% of the global population of people living with HIV (PLHIV) is located in Africa alone. Of this proportion of PLHIV in Africa, an estimated three-quarters are women of reproductive age living with HIV in the Sub-Saharan region of Africa (Dwyer-Lindgren et al., 2019; Hutchings & Potterton, 2014; World Health Organization, 2018). In 2018 the World Health Organization (WHO) estimated that 1.1 million pregnant women living with HIV worldwide received antiretroviral therapy (ART) for the prevention of mother-to-child transmission (PMTCT) (World Health Organization, 2018). Of the 1.1 million pregnant women living with HIV worldwide, who received ART for PMTCT, an estimated 31% were from South Africa. When South Africa's estimated percentage is compared with those from other neighbouring countries such as Mozambique which had 15%, Zimbabwe (19%) and Malawi (24%), South Africa has the highest estimate of pregnant women living with HIV , who received ART for PMTCT (Dwyer-Lindgren et al., 2019; World Health Organization, 2018). The age category 15-49 years encompasses women of childbearing age, which has hence influences the future population at large (Isah et al., 2017).

PMTCT has increasingly empowered women living with HIV to be able to make informed decisions relating to fertility intentions, and the health of their unborn infants (Burton et al., 2015). The successful uptake of PMTCT in South Africa as of 2002 has enabled women of this population to carry multiple pregnancies to term with dramatically lower risks of perinatal vertical transmission during pregnancy and postpartum (Burton et al., 2015). There has hence been a continued positive increase in the prevalence of HIV exposed but uninfected (HEU) infants. Given that the incidence of vertical transmission is <5% in South Africa, >95% of HIV exposed infants remain uninfected (Filteau, 2009; UNAIDS, 2019). Globally as of 2018, there is a total of ~14.8 million HEU children (0-14 years). Approximately 72% of this total of HEU children are in Sub-Saharan Africa and a third (3.5million) are in South Africa alone (UNIAIDS, 2019). HEU are a growing population of children in South Africa, with heighted negative health outcomes such as increased morbidity and mortality, as well as delayed development (Filteau, 2009)

During the early years of an infant's life, developmental milestones must be achieved. Milestone categories or domains include : (i) communication (ii) cognitive development (learning abilities, problem solving) (iii) social and emotional development and (iv) movement and physical development (gross motor and fine motor), (Hutchings & Potterton, 2014). Differences in the early development of HIV unexposed and uninfected (HUU), HIV exposed and infected (HEI), and HEU infants have been extensively researched regionally in Southern Africa, but research has focused primarily on the negative neurodevelopmental outcomes of HEU and HEI infants (Springer et al., 2018) . For example, a study by Hutchings & Potterton, (2014) with HEU and HEI infants aged 6 weeks to 12 months in Zimbabwe suggested that HEI infants are more likely to experience developmental delay compared to HEU infants. In addition, research has compared the development of HEU versus HUU infants, with HEU infants having slight delays in neurodevelopment, including poor cognitive and motor function which can lead to learning difficulties in terms of physiological function, and delayed communication i.e. language development (Springer et al., 2018).

The delay of early infant development in one or more developmental domains can be attributed to direct and indirect exposures to multiple risk factors in-utero and postpartum (McCoy et al., 2016a). For HEU infants, the neurotrophic effects of exposure to HIV and antiretroviral (ARV) drugs from PMTCT as well as limited breastmilk exposure from mothers is associated with delayed development (Filteau, 2009).

In addition to biological factors which may be confounded by genetic composition, psychosocial factors may have important effects on early child development (McCoy et al., 2016a). For example, early experiences relating to the responsiveness of a mother-infant relationship, and other important stimuli in their environment contribute to the physical, cognitive, emotional, and social development of infants (Logan,et al., 2007). In addition, early experiences such as a mother's intention to conceive at the point of conception play a pivotal role in how the mother, the pregnancy and the infant develop (Logan et al., 2007; Mughal et al., 2018).

The intention of pregnancy of WLHIV is a potential risk factor for HEU children's early infant stage development, and is critical for epidemiological research in HIV/AIDS (Joyce et al., 2000b). Unintended pregnancies are a public health concern and ~44% of pregnancies globally are documented as unplanned/unintended (Iyun et al., 2018). These are live pregnancies, which

are considered mistimed or undesired with or without the use of a contraceptive method at the point of conception (Logan et al., 2007).

Africa has high rates of unintended pregnancies of up to 62%, with women who are newly initiated on ART being more likely to have an unplanned pregnancy thereafter (Adeniyi et al., 2018). Even with the wide availability of family planning services in public health facilities, as little as 35% of pregnancies among women living with HIV are planned in Sub-Saharan Africa (Brittain et al., 2019; Iyun et al., 2018). In Southern Africa this is most especially observed in South Africa, which has a high prevalence of early sexual debut irrespective of status, which is added to by early HIV transmission in young girls and women overall (Brittain et al., 2019; Cooper et al., 2007). South African WLHIV are six times more likely to have an unintended pregnancy than women living with a negative HIV status (Brittain et al., 2019; Iyun et al., 2018).

Circumstances leading to unplanned pregnancies are similar amongst all women irrespective of HIV status (Logan et al., 2007). It is known that unintended pregnancies are more common amongst adolescent and younger mother below ~24 years of age (Cooper et al., 2007; Joyce et al., 2000a). These women are most likely to be single, and from a poorer socioeconomic, and educational background (Joyce et al., 2000a; Logan et al., 2007).

The health outcomes of unintended pregnancy, and their consequences may have negative adverse effects on the infants born of the pregnancies with risks such as preterm birth, low birth weight <2500g, and ultimately long-term developmental delays (Logan et al., 2007; Stein et al., 2014). The consequences associated with unintended pregnancies have been known to include perinatal mental health issues (e.g. depression), late stage booking into antenatal care, substance abuse, and intimate partner violence, and elevated stress or strain (financial, and general welfare) (Logan et al., 2007; Stein et al., 2014). Unintended pregnancies have also been associated with socioemotional issues in mother infant relationships (Stein et al., 2014). These issues can result in weak bonding, sensitivity issues (inadequate time and attention hence unresponsiveness, or intrusiveness/controlling parenting), which in the extreme can lead to child abuse on the mothers part (Filteau, 2009; Stein et al., 2014).

Women's' feelings about their pregnancy and relationship with the infant born of the pregnancy play a large role in the quality of caregiving (Cheng et al., 2009; Logan et al., 2007). Investigations into the association of pregnancy intentions, and early infant development have

been explored in the past in western developed countries, USA, and European countries such as Finland (Joyce et al., 2000a). These studies did not find a significant association between the intention of the pregnancy and child development (Joyce et al., 2000a; Joyce et al., 2000b). However, a study of the trajectories of maternal stress and anxiety from pregnancy to 3 years in Canada found an association between maternal stress and anxiety, and child development measured at 3 years, however in this cohort the women's HIV status was not included (Mughal et al., 2018).

Rationale for the proposed study

Research into pregnancy intentions is widely required to inform the growing pool of knowledge for evidence-based practices in integrated routine care targeted at the WLHIV and infants affected (Filteau, 2009; Logan et al., 2007; McCoy et al., 2016a). The majority of research has focused primarily on associations between pregnancy intentions, and variables such as HIV status, mental health of the women, adherence and viral load suppression, cost burdens of pregnancy as well as physical growth outcomes of infants (Brittain et al., 2018; Iyun et al., 2018). However, no studies of the association between pregnancy intentions of WLWHIV and the early development of their HEU infants across developmental domains could be identified in the existing literature.

Despite this lack of evidence, pregnancy intentions have been found to be associated with maternal stress and anxiety which in turn is associated with negative outcomes for child development (Cheng et al., 2009). HEU infants are a vulnerable group, and additional research into early life exposures which may influence early developmental risk factors aligned to their mother psychosocial issues (Filteau, 2009). As such, there is a need for analytical research to determine the association between the intention of the pregnancy of WLHIV and the early development of their HEU infants.

The proposed study will give insights into variations in development of HEU infants according to the pregnancy intentions of their mothers. The outcomes of this analysis will potentially highlight the continued importance of targeted interventions for integrated family planning services for WLHIV (Gruskin et al., 2008; Myer et al., 2018). As well as the possible need for early psychosocial interventions for women of reproductive age living in communities with high burden of HIV and high incidences of unplanned pregnancies (Gruskin et al., 2008). In

addition, this research may highlight the need for early paediatric development interventions for HEU infants in these same communities.

Purpose of the study

The purpose of the study is to examine if the intention of pregnancy of WLHIV is significantly associated with the development of their HEU infants.

Research question

"Is the intention of pregnancy of mothers living with HIV associated with the early child development of their HEU children?"

Exposure: Unplanned pregnancy of mothers
Comparison: Planned pregnancy of mothers
Outcome: Child development for HEU children aged between 36-60 months

Aims and Objectives of the study

Aim

The aim is to carry out secondary data analysis to determine the association between early childhood development of HEU infants aged 36-60 months and the intention of pregnancy of their HIV positive mothers.

Objectives

- To describe the intendedness of pregnancies among women who initiated ART during pregnancy.
- To explore the association between the intendedness of the pregnancy and early child development at 36-60 months postpartum.

Methodology

Study design

The data that is going to be used in this study is from the "Long-term Adherence and Care Engagement" (LACE) study (May 2017-April 2018). The LACE study consisted of a single follow-up visit after the "Maternal-Child Health Antiretroviral Therapy" (MCH-ART) study (completed in 2016). The MCH-ART study enrolled WLHIV who were initiating ART during pregnancy and followed them through delivery. Women who then opted to breastfeed were randomly allocated to postpartum models of ART care and were followed through 12-18

months postpartum. The LACE study then aimed to assess longer-term outcomes among these women and their children, including the major biological, behavioural and health service determinants of these outcomes.

The proposed study is a cross sectional sub-study using data from the mother-child pairs who attended this additional study visit for LACE.

Characteristics of the study population

Postpartum women living with HIV >18 years of age previously recruited for the MCH-ART (completed in 2016) and LACE (completed in 2018) studies, at the Gugulethu Midwife Obstetric Unit in Cape Town.

Inclusion criteria

- Aged >18years
- Fully consented pairs of WLHIV and their HEU children recalled for interviews for the LACE study (May 2017-Apr 2018)
- Attended and completed the Ages and Stages Questionnaire (ASQ) and the London Measure of Unplanned Pregnancy (LMUP) Questionnaire at study visits

Exclusion Criteria

- Women who attended the study visit without their infants for developmental screening.

Recruitment and enrolment

- For the LACE study, mother-infant pairs who had been enrolled into postpartum follow-up for the MCH-ART study were invited to participate in a single follow up study visit. The women had previously consented to future contact for related research studies as part of MCH-ART. Informed consent was obtained from all women who attended the LACE study visit.
- The participants for the proposed study are a sample of the population recruited as part of the LACE study who consented, attended one study visit as mother child pairs, and completed the questionnaires, which will be used for this analysis.

Research procedures and data collection method

- All the data to be analysed for this study will be extracted from data collected during the LACE study.
- Trained research interviewers administered questionnaires in isiXhosa or English. All measures had been validated for use in the South African context.

- To measure the pregnancy intention of the women, The London Measure of Unplanned Pregnancy (LMUP) questionnaire was administered at enrolment into the MCH-ART study. The tool assesses the retrospective circumstances of the most recent pregnancy, and the women's family planning methods prior to the pregnancy (Barrett et al., 2004; Hall et al., 2017). The questionnaire is made up of six questions relating to timing of pregnancy, contraceptive use, the desire of the women and of the partner and planning (Barrett et al., 2004). Each question is scored between 0 and 2 and is totalled for a final score of 0-12. Scores can be categorized as: 0–3 (unplanned/unintended), 4–9 (ambivalent); and 10–12 (planned/intended), (Barrett et al., 2004; J. Hall et al., 2017).

- Outcomes of development milestones can be measured using standard screening tools such as clinically administered questionnaires, or self-administered questionnaires by caregivers during routine care. For early child development, The Ages and Stages (ASQ) standardized developmental screening tool for children under 5.5 years of age was administered with mother-child pairs at the LACE study visit. The ASQ has previously been standardised for use in clinical studies in Southern Africa (Hsiao et al., 2017) .The ASQ-3 assessed overall development across 5 domains: communication, gross motor, fine motor, problem-solving, and personal-social functioning. The ASQ: SE-2 assessed social-emotional development of the infant. Both the ASQ-3 and ASQ: SE-2 were administered to each mother-child pair, with the appropriate component of each selected based on the child's age. The tool was designed to be used by parents or lay health professionals (Squires et al., 1997).

- Each questionnaire has a standardized scoring sheet, with responses being "Always/Often", "Sometimes", or "Rarely/Never". Each response can take up a score value of either '0', '5' or '10'depending on the question. Cut-off scores vary per infant age and domain. For the ASQ-3, higher scores indicate a lower risk of delay and hence better development, whilst below the cut-off score, development is high risk for delay and hence poorer development. The high-risk score range has two possible outcomes for guidance: 'Monitor' or 'Refer'. For the ASQ: SE-2, lower scores indicate a lower risk of delay and hence better development, whilst above the cut-off score, development is considered poor and hence high-risk. The high-risk score range also has two possible outcomes for guidance: 'Monitor' or 'Refer'. For this analysis, scoring will follow standardized guidelines and cut-off scores for developmental delay.

- For maternal and infant socio-demographic characteristics, an additional questionnaire was administered to collect data. The Socio-demographic characteristics assessed for the women included Age, socio-economic status (SES), education, marital status, and poverty. Clinical characteristics assessed included: Nulliparous (never been pregnant), gestational age at enrolment and if they were newly diagnosed with HIV during the pregnancy. For infants, demographic characteristics included age, gender and whether infants were born preterm

Table 1: Table of Baseline characteristics of the women and infants

	Total (n)	Frequency (n)%
Women		
Median age		Numerical (IQR)
<25 years		Categorical
25-35years		
>35 years		
Completed secondary/any tertiary		
SES		Categorical
Employed		Categorical
Married or co-habiting		Categorical
Newly diagnosed with HIV		Categorical
Nulliparous		Categorical
Gestational age at enrolment (weeks)		Categorical
Infant		
Median age (IQR)		Numerical (IQR)
		Categorical
Female		Categorical
Born full term		Categorical
Low birth weight (<2500g)		Numerical (IQR)
		Categorical

Table 2: Data analysis Dummy table with variables of Interest

	Total (n	Frequency (n)%	
Women			
LMUP score			
Unplanned (0-3)			Numerical (IQR)
Ambivalent (4-9)			Numerical (IQR)
Planned (10-12)			Numerical (IQR)
Infants			
			Numerical (IQR)
ASQ 3		**Delayed**	**Not delayed**
Gross Motor			
Fine Motor			
communication			
Problem solving			
Personal social			
ASQ 2			
Social emotional			

Data analysis

*Data will be exported to STATA v15.0 (*Stata Corporation, College Station, Texas, USA*) for analysis.*

- The data will be described using proportions with 95% confidence intervals for categorical variables and means with standard deviations or medians with inter-quartile ranges for continuous variables, as appropriate.
- For associations, Rank sum or Chi-squared test (Categorical variables) and Wilcoxon sign rank or Kruskal Wallis (Non-parametric -Continuous variables) and ANOVA or t-test (parametric data) will be used.
- These tests will be used to compare the possible associations between intention of pregnancy (unintended vs intended) on early child development of children between the ages of 36-60 months (above ASQ cut-off (classified as Normal) vs below ASQ cut-off scores (Classified as delayed)).
- *A priori* Confounders such as mother's age and SES, infant's age and gender will be adjusted for if necessary during analysis.
- The responses for intention of pregnancy will then be compared within subgroups of women based on demographic, clinical and psychosocial characteristics.
- Whilst early child development will be compared in subgroups of mother's pregnancy intention and infant demographics such as gender
- Regression model analysis (Bivariate and Multivariate) will be carried out for the intention of pregnancy of the mother vs the developmental outcomes of the HEU infants

Data safety and monitoring

- Data collected for LACE on paper forms was entered into a custom designed Microsoft Access database, maintained in a firewall-protected UCT server with nightly backups.
- The LACE study database was password-protected following standard password safety procedures.
- All study records contained anonymous participant identification numbers, and no participant names or identifiers were recorded.
- For this proposed study, no data with personal identifiers will be used and data will not be reported on individuals
- Data will be exported from the database and stored in a password-protected folder for the study analysis.

Ethics

- The protocol for the proposed study will be presented for review and approval with the University Of Cape Town Faculty Of Health Sciences Human Research Ethics Committee (UCT-HREC) before data analysis can commence.
- The MCH-ART and LACE study protocols, informed consent forms, and all data collection tools were previously reviewed and approved by the Columbia University Medical Center Institutional Review Board (CUMC-IRB) and the University Of Cape Town Faculty Of Health Sciences Human Research Ethics Committee (UCT-HREC). After the initial review and approval, the CUMC-IRB and UCT-HREC reviewed the progress of the study annually.

Risks and Benefits

Risks

- As this study involves only secondary analysis of data, the only risk to participants is the loss of confidentiality.
- Measures were previously implemented in order to minimize risk in the LACE study and will carry over into the proposed study. All study records contain anonymous participant identification numbers, and no participant names or identifiers will be used.
- Only the previously collected data from the parent study will be used for secondary data analysis. No new data will be collected for this study.

Benefits

- Any inferences from the data will inform and highlight the importance of unplanned pregnancies amongst the WLHIV and using services at Gugulethu Midwife Obstetric Unit. This will also provide insight for integrated routine care for maternity, family planning services and pediatric care in Cape Town, South Africa.
- The findings will inform society's knowledge of unplanned pregnancies particularly in HEU infants. The findings will inform society on the increased need for education and awareness of the consequences of unplanned pregnancy on infants and the importance of early interventions for delayed developments by caregivers.
- The outcomes of this analysis will potentially contribute to ongoing research for reproductive health services, PMTCT, and early child development services. The findings will highlight the continued importance of targeted interventions for integrated family planning services for women living with HIV from similar contexts in and around South

Africa, which could potentially be integrated with early pediatric development interventions for HEU infants.

Informed consent

Participants for the MCH-ART and LACE studies signed informed consent forms (ICF). ICF forms were delivered in participants' home language (isiXhosa) by trained interviewers. The ICF detailed the purpose of the study, study procedures, and the risks and benefits to the women and children.

- Participation was voluntary, and their choice regarding participation in no way influenced the quality of routine medical care for women or their infants.
- Women could choose to exit the study at any time for any reason without compromising the quality of health care received for the women and their children.

Budget

The proposed project will not require a budget.

Timelines

Task	Duration					
	2019				2020	
	Sept	Oct	Nov	Dec	Jan	Feb
Literature review						
Clean and check data sets						
Data analysis						
Draft Write-up						
Complete Write Up						
Submission						

Dissemination of results

The proposed project will be disseminated in the form of a Master of Public Health thesis and a journal manuscript in line with the requirements for the MPH degree.

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PART B: STRUCTURED LITERATURE REVIEW

Introduction

The largest burden of HIV/AIDS in the world is in the Sub-Saharan region of Africa, and the majority of people living with HIV are women of childbearing age. Within the region, the eastern and southern countries alone are home to over 50% of the global population living with HIV (Pandey & Galvani, 2019). South Africa as a country holds over a quarter of the HIV burden with 7 million people living with HIV (World Health Organization (WHO), 2016). HIV/AIDS disproportionately burdens the female population with 4.5 million women of reproductive age living with HIV in South Africa (Dwyer-Lindgren et al., 2019; World Health Organization (WHO), 2016).

In 2018, South Africa and Nigeria had the highest proportion of women initiated on antiretroviral therapy (ART) globally, with 31% of the 1.1 million initiated on ART being women from South Africa and 28% being women from Nigeria (Dwyer-Lindgren et al., 2019). The increase in access and coverage of ART, including through prevention of mother-to-child transmission (PMTCT) programmes in Africa, has resulted in the reduction of vertical transmission, and hence an increase in the percentage of HIV exposed and uninfected (HEU) infants (Le Roux etal., 2016). This has thereby drastically reduced the number of new infections among infants born to WLHIV to below 5% (Rotheram-Borus et al., 2019; Webb et al., 2018).

The population of HEU children in South Africa increased from approximately 700 000 in 2002 to above 3.5 million in 2018 (UNAIDS, 2019). With continued growth of this population of interest it is key to understand the associations between poor health outcomes, and various biological, psychosocial and environmental exposures (Filteau, 2009). For example, it is known that maternal perinatal exposures such as maternal depression can have negative outcomes for the mother and the child (Skeen et al., 2014).

Objectives

This review aims to identify and summarise key literature relating to the effect of pregnancy intention on child development across developmental domains, as well as briefly summarise key literature relating to screening interventions for early child developmental delay. The scope of this review will expand and examine knowledge relating to the key themes of the proposed research question. As well as highlight, the gaps in research related to the pregnancy intentions of WLHIV, and the development of their HEU infants in sub-Saharan Africa and particularly South Africa.

Search Strategy

The literature search was conducted in PubMed and Google Scholar, with additional relevant articles identified in references lists. Search terms were selected based on the study objectives and included **"Global HIV burden", "PMTCT AND HEU", "Risk factors for Child development", "Pregnancy intention OR unintended pregnancy AND WLHIV" , "Child development domains AND screening", "Ages and Stages".** The initial search included global literature, which was later narrowed to include Africa, Sub-Saharan Africa and then South Africa.

Summary of Literature

Unintended/Unplanned pregnancy

Unintended pregnancies are live pregnancies which are considered mistimed or undesired (Logan et al., 2007). Over the past two decades, the intention of pregnancy of WLHIV has been of interest in academic research globally, and the intention of pregnancy of WLHIV is a potential risk factor, and a continued challenge for PMTCT (Feyissa et al., 2019). Understanding the fertility desires of WLHIV contributes to the knowledge base for targeted health services strategies and interventions (World Health Organisation, 2010). These align with WHO comprehensive approach strategies for PMTCT , which aim to prevent HIV infection and transmission, unintended pregnancy and provide appropriate treatment and care (World Health Organisation, 2010).

Globally, the prevalence of unintended pregnancy was as high as 44% in 2018 (Iyun et al., 2018; Joyce et al., 2000). Africa has high rates of unintended pregnancies of approximately 35%, with a particularly high incidence among WLHIV who are newly diagnosed and initiated on ART (Adeniyi et al., 2018; Feyissa et al., 2019). An earlier study in the South African context carried out by Schwartz et al., (2012) found that 62% of the sample of WLHIV on initiated on ART reported unplanned pregnancies after initiation. This similarly mirrors a finding of 60% from a recent study by Brittain et al., (2019) whose sample consisted of WLHIV initiated on ART. Even with the wide availability of family planning services in public health facilities, as little as 30% of pregnancies among WLHIV are planned in Sub-Saharan Africa (Brittain et al., 2019; Iyun et al., 2018).

The circumstances leading to unintended pregnancies are similar amongst all women irrespective of HIV status (Logan et al., 2007). Evidence suggests that unplanned pregnancies

are more common amongst adolescent and younger women below ~24 years of age (Cooper et al., 2007; Joyce et al., 2000). These women are most likely to be single, and from a poorer socioeconomic and educational background (Joyce et al., 2000; Logan et al., 2007). Other risk factors for unintended pregnancies include a lack of contraceptive use or failure of a contraceptive method, limited pregnancy awareness, and sexual assault (Feyissa et al., 2019) . These risk factors are especially important in South Africa, which has a high prevalence of early sexual debut and sexual violations (Cooper et al., 2007), leading to a high incidence of early HIV transmission to young girls and women as well as unintended pregnancy (Cooper et al., 2007). Conclusions from research by Iyun et al., (2018) highlighted how a sample of South African WLHIV are more likely to have an unintended pregnancy, than women who are HIV negative. Whilst WLHIV who are married or in a relationship with the support of a partner towards contraceptive are more likely to plan a pregnancy (Brittain et al., 2019).

Unplanned pregnancy have adverse health outcomes such as infant preterm birth, low birth weight and prolonged development (Stein et al., 2014). Whilst perinatal mental health issues such as drug or alcohol use, depression, Intimate partner violence, stress and delay in antenatal booking for care (Stein et al., 2014).

As such lack of positive feelings towards parenting can result in minimal responsiveness to infant development needs, as well as weak infant-parent attachment, which can lead to adverse events such as child abuse (Filteau, 2009; Stein et al., 2014).

Research has established significant associations between depressive symptoms and unintended pregnancy (Brittain et al., 2018). Long term effects of this association have an effect on socio-emotional domain as well as the domains such as problem solving, and personal-social which are dependent on cognitive development (Logan et al., 2007; Skeen et al., 2014).

Haffejee, et al. (2017) conducted a study in public health facilities in Kwa-Zulu Natal investigating unintended pregnancies, and found that being married was significantly associated with a planned pregnancy. In the same population, HIV status was reported to not influence the women's desire to have children. Lack of contraceptive use was significantly associated with unintended pregnancy, largely related to minimal understanding of reproductive health and contraceptive use (Haffejee et al., 2017).

Development

Development during the first 5 years of a child's life is critical, and detection of unmet developmental milestones should be identified early to initiate intervention before delay becomes adverse (McCoy et al., 2016a). Development encompasses physiological, psychological, socio-emotional and biological growth(Grantham-McGregor et al., 2007). Milestones must be met across several domains, which constitute all aspects of a child's development(McCoy et al., 2016b). Developmental domain include:

Table 1: Key six developmental domains for early child development

	Developmental domain	**Components of domains**
(i)	Communication	Gestures, sounds, response and verbal ability
(ii)	Problem solving	Cognitive development ,key for learning and understanding, as well as decision-making
(iii)	Fine motor skills	Movement and physical development. The coordination of small and large muscles (e.g.) holding object with hands, blinking, Crawling, running
(iv)	Gross motor skills	
(v)	Personal Social	Self-efficacy, confidence, social interactions
(vi)	Social and emotional development	Lead to emotional regulation, relationships

(Hutchings & Potterton, 2014).

Prolonged delay in one or more of these domains can have far-reaching effects, including the risk of later learning difficulties in infants who had cognitive delays (Hutchings & Potterton, 2014). Children from low- and middle-income countries (LMICs), including South Africa, are the most vulnerable and at risk of developmental delay (Grantham-McGregor et al., 2007). Approximately 250 million children in developing countries are developmentally delayed (Black et al., 2017). Development is stimulated by the child-parent relationship (Nelson & O'Brien, 2012). This relationship is the earliest relationship and interaction which influences the response of an infant to stimuli, particularly within the personal-social and emotional domains (Nelson & O'Brien, 2012). A major risk factor for delayed or poor developmental outcomes in children from vulnerable communities in South Africa is exposure to HIV/AIDs

(Hall et al., 2017; Springer et al., 2012). Absences of a parent due to death from HIV/AIDS is devastating to the development of an infant left orphaned (Cluver et al., 2013; Filteau, 2009). The quality of care is compromised and there is minimal or no possible relationship with a biological parent (Cluver et al., 2013). Poverty in South Africa is strongly associated with the inability to pursue education, with a high population of school drop outs and employment (Haffejee et al., 2017). As a result there are psychological disruptions related to the outcomes of poverty among women from strain and distress (Haffejee et al., 2017).

In addition, the neurotrophic effects of exposure to HIV and antiretroviral (ARV) drugs from PMTCT as well as limited breastmilk exposure from mothers among HEU infants has been associated with delayed development (Filteau, 2009).

Screening

Developmental tools are used to identify a child's deviation from the developmental norm of their age group, and thereby reduce mortality and morbidity due to developmental delays (Naidoo & Avenant, 2018; Van Der Linde etal., 2015). The tools utilised systematically identify signs of developmental delay (Van Der Linde et al., 2015). Most countries globally use their own standardised screening tools for assessment (Van Der Linde et al., 2015). To assess child development in South Africa in National Public health facilities there is the "Road to Health Booklet" (RTHB) which is used to record developmental data across milestones by Health workers and caregivers during paediatric visits for children between 0-5 years old (Naidoo & Avenant, 2018).

In developed countries, the screening tools used have higher sensitivity to identify high risk infants and higher specificity than the RTHB (Small et al., 2018; van Der Linde et al., 2015). Key western developmental assessment tools include the Bayley's Scales of Infant Development (III) and the Ages and Stages (ASQ), (Hsiao et al., 2017; Van Der Linde et al., 2015). These tools measure early development of children at varied ages from birth across developmental domains (Gladstone et al., 2007). They comprise of specific domain questions whose responses are scored on a scale range. There is also a cut-off point or score for each level of development, allowing the identification of children who are at risk of developmental delay (Van Der Linde et al., 2015).

Bayley's (III) is considered a gold standard for infant developmental assessment studies in Southern Africa and is highly used in clinical studies in developing countries to assess

development, but must be administered by clinically trained researchers (Hsiao et al., 2017; Rakotsoane et al., 2017). In contrast, parents or other caregivers can complete the ASQ, with responses based on the observations made of a child (Squires et al., 1997). Although the ASQ has been standardised for use in South Africa, it is costly to use in public health clinics and requires substantial time per infant (Squires et al., 1997; Van Der Linde et al., 2015).

Comparing the outcome of assessment of the ASQ versus the RTHB in South Africa, the western developed tool assesses more developmental domains (Van Der Linde et al., 2015). This is regardless of the children's age intervals and provides clear scores and guidelines for further evaluation which the RTHB fails to do (Bricker et al., 1999; Van Der Linde et al., 2015). For example, the RTHB doesn't assess social- emotional/Behavioural domains and is not ideal for research purposes (Naidoo & Avenant, 2018; Van Der Linde et al., 2015). In addition, the RTHB has low sensitivity for the detection of adverse outcomes, and hence the use of a high sensitivity tool is required to detect symptoms of developmental delays for referral and intervention (Naidoo & Avenant, 2018; Van Der Linde et al., 2015).

Overall, the ASQ is widely known for its validity in screening and testing of developmental characteristics of children at primary health care level, and where available is a useful tool for developmental assessment among infants in clinical studies (Small et al., 2018; Squires et al., 2015; Van Heerden et al., 2017). There is therefore a need for extensive research in LMIC using highly sensitive, validated tools for screening in clinical studies (Rakotsoane et al., 2018). This is necessary to truly determine and investigate the risks and burden of early infant developmental delays and, contribute to the development of intervention strategies and improvement of measurement tools particularly in LMIC's (Squires et al., 2015).

HIV Exposure and Infant Development

With the implementation of universal ART coverage as well as other ART services , there have been major reductions in mother-to-child transmission (MTCT) among pregnant women living with HIV (Afran et al., 2014). Alongside these successes, concerns have been raised regarding the health and development of HEU infants, including poorer growth and higher levels of morbidity (le Roux et al., 2016). In particular, HEU infants are at an increased risk for developmental delay when mothers have severe disease progression, and limited ART use for PMTCT (Le Roux et al., 2016).

Early stage development among HEU infants is critical for epidemiological research in HIV/AIDS (Joyce et al., 2000a). It is important for the identification of risk factors for delayed development among HEU, and the quantification of the burden on a population scale (Joyce et al., 2000a). All which can inform early interventions such as screening, and hence referral for diagnosis and treatment or therapy (Joyce et al., 2000a). Over the past two decades, there have been numerous contributions from studies to the evidence base (Joyce et al., 2000a). These studies have extensively analysed the effects of biomedical and environmental factors on the health outcomes of mothers and their infants, but have focussed largely on comparing HUU and HEI children (Grantham-McGregor et al., 2007; Sherr et al., 2014). Although these studies have been key for interventions and resource allocation towards understanding and supporting the development of this vulnerable population (Rotheram-Borus et al., 2019). A better understanding of these issues among HEU children has historically been lacking.

In recent years, studies have begun to focus more on this growing population of HEU children (Filteau, 2009; Myer et al., 2016; Patel et al., 2010). Studies have focused on developmental domains, which relate to future learning abilities for education such as neurodevelopment and cognitive functions of HEU children (Springer et al., 2019). For example, a study of HEU and HEI infants aged 6 weeks to 12 months in Zimbabwe found that compared to HEU infants, HEI infants are more likely to experience developmental delay in cognitive, language and motor developmental domains (Hutchings & Potterton, 2014). In addition, research in South Africa has compared the development of HEU versus HUU infants, with HEU infants having slight delays in neurodevelopment, including poor cognitive and motor function which can lead to learning difficulties in terms of language development and physiological function (Springer et al., 2018).

However, there is also evidence to suggest that early child development is driven by environmental and social factors, regardless of HIV status. For example, a cohort study of children aged 6-18 months in India concluded that the development of HIV exposed infants was confounded by risk factors such as poverty (Rajan et al., 2017). These findings were supported in a study comparing the development of HEU and HUU infants in South Africa (Springer et al., 2012). Springer, et al (2012) used the Bayley's (III) to determine if there was a difference in the development of HEU and HUU infants below 3 years of age. These findings were from data collected and analysed among infant cohorts from Europe as well as Africa(Springer et al., 2012). The outcomes of the study concluded no differences in the scores

between the two groups of interest. The results of a systematic review support this, with Fileatu (2009) also concluding that developmental delays in HEU infants are not attributed to in-utero exposure to HIV, but rather to environmental factors.

Given these findings, some research within South Africa has explored the association of key biological, psychosocial and environmental risk factors such as the mother's mental health, intimate partner violence, substance abuse and social economic status on health outcomes (Donald et al., 2018; Rotheram-Borus et al., 2019). In addition, there is an increased interest in the health outcomes of WLHIV and their HEU children with regards to their paired relationship and interaction for infant development (Moehler et al., 2006). For example, Springer, et al (2012) spoke of the association between mother's postnatal depression and child development, which is a highly researched aspect from not only the biomedical view, but also the behavioural and socio-emotional.

Main exposures have been identified as biological and environmental factors, but there has been minimal exploration of their effect on overall child developmental domains including the socio-emotional domain (Feldman & Eidelman, 2009; Springer et al., 2012; Strehlau et al., 2018). As mentioned by McCoy et al. 2016a development in all domains is crucial for individuals to reach their full developmental competency for "behavioural, socio-emotional, academic and economic accomplishments". Prolonged infant delays result in the increased potential risk of reduction to future optimal economic capability of adult individuals (McCoy et al., 2016b).

Association between unintended pregnancy and development

The majority of research to date has focused primarily on the investigation of the association of intention of pregnancy with variables such as HIV status, mental health of the women, adherence and viral load suppression, the cost of burden of pregnancy as well as physiological growth of infants (Brittain et al., 2018; Iyun et al., 2018). However, there has been few investigations into the association between unintended pregnancy and early child development in Sub-Saharan Africa, despite the high prevalence of unintended pregnancy and a 44% prevalence of delay in early child development in Africa (Feyissa et al., 2019; McCoy et al., 2016a). Studies that have investigated this association in Western developed countries have found no significant association between the intention of the pregnancy and child development (Joyce et al., 2000; Joyce et al., 2000).

Genetic composition, psychosocial factors and environmental factors may have important effects on early child development (McCoy et al., 2016a). Previous research has investigated the association of with related psychosocial factors with infant development. For example, Logan (2007) explored early experiences relating to the responsiveness of a mother-infant relationship and its effect on the physical, cognitive, emotional and social development of infants (Logan et al., 2007). In addition, early experiences such as a mother's intention to conceive at the point of conception play a pivotal role in how the mother, the pregnancy and the infant develop (Logan et al., 2007; Mughal et al., 2018).Although there isn't sufficient evidence from research indicating a relationship between delayed development and unintended pregnancy (Logan et al., 2007). However there is evidence of the relationship between unintended pregnancy with a delay in seeking antenatal care, and prenatal maternal behavioural outcomes (Logan et al., 2007)

Unintended pregnancy has been linked to low levels of breastfeeding which in turn may be associated with impaired maternal bonding (Nakano et al., 2019), while being a first time mother has also been linked to impaired bonding (Feyissa et al., 2019; Joyce et al., 2000). The importance of maternal bonding with regards to child development can later affect domains such as personal social and socioemotional which rely on early relationships(Joyce et al., 2000).

In countries such as Finland, and the USA, have explored the relationship of pregnancy intentions and early infant development (Joyce et al., 2000). However, results were not a significant, whilst study in Canada found an association between maternal stress and anxiety in women without HIV (Joyce et al., 2000a; Joyce et al., 2000b; Mughal et al., 2018).

Conclusion

The knowledge surrounding the health seeking behaviour of WLHIV are essential for developing appropriate family planning and reproductive services targeted at WLHIV ,(World Health Organisation, 2010). Intention of pregnancy is an ongoing concern in sub-Saharan Africa, particularly in South Africa as unplanned pregnancy is a risk factor for MTCT among pregnant women living with HIV (Feyissa et al., 2019). It is therefore paramount for the consequences of unintended pregnancy among WLHIV to be further investigated.

Strides in PMTCT success have led to the increase in the prevalence of the HEU infant population (Springer et al., 2018). The ability to meet early developmental milestones from

birth to the age of 5 years is crucial for all infants (McCoy et al., 2016a). Collection of data for infant development in LMIC's is essential to highlight the need for intervention development to support the development of infants (Grantham-McGregor et al., 2007). The usage of standardised tools is considered ideal for data collection due to their high specify and high sensitivity. Of the studies included in this review, the majority made use of the ASQ or the Bayley's (III) among samples of infants from various countries, ages, and exposure to HIV (Van Der Linde et al., 2015). HEU infants require in-depth analysis of research data for evidence based contributions towards policy and, services aligned to infant development support and care in SSA (Springer et al., 2018)

Due to the mentioned paucity of data in literature, there is therefore a gap for the exploration of the effect of maternal psychosocial risk factors of WLHIV's behavioural outcomes related to pregnancy (Lachman et al., 2019). Research investigations are therefore required to explore the intention of pregnancy of WLHIV as a potential risk factor of delayed early infant development.

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PART C: JOURNAL MANUSCRIPT

Journal Abstract

Unplanned pregnancies continue to be a challenge towards the on-going strides and achievement of prevention of mother-to-child transmission (PMTCT). There is however a paucity of data for research for the effect of unplanned pregnancy and early child development in South Africa. This study focused on early infant development outcomes of HIV exposed but uninfected (HEU) infants. The aim of the study was to investigate the association between the intention of pregnancy among pregnant women living with HIV (WLHIV) *(n=250)*, and the subsequent early development of their HEU infants in Gugulethu, South Africa. The median age for women in the study was 28.3 years. Based on the women's responses from The London Measure of Unplanned Pregnancy (LMUP) questionnaire, 58% of pregnancies were categorised as unplanned, whilst 21% of the women scored high towards intendedness (planned), and 21% scored in the mid-range for ambivalence.

Overall, infants with evidence of early developmental delay that scored below threshold (ASQ-3) were 8% for the gross motor domain, 19% for fine motor, 4% for communication, 15% for problem solving, and 7% for personal social domain. Whilst for the social emotional domain (ASQ: SE-2), two percent of infants scored above threshold and hence, had evidence of early developmental delay. Using multivariate linear regression models, no significant associations were observed between the women's pregnancy intentions and the early development of their infants in any developmental domain ($P>0.05$).

Limitations of the study include recall bias from the retrospective responses of questionnaires as well as a small sample size. The findings of this research accentuate the need for targeted strategies towards psychosocial issues, and educational interventions for WLHIV and, for informed fertility decisions. Furthermore, the need for exploration of interventions to encourage infant-parent attachment and interaction for development, as well as the impact of pregnancy intentions on parenting behaviours.

Keywords: Unintended pregnancy, Infant development, HEU, South Africa, Psychosocial

**Abstract is in accordance with guidelines for The Child and Maternal Journal.*

Introduction

The increase in access and coverage of maternal antiretroviral therapy (ART) in Africa among other factors has resulted in the reduction of vertical transmission, and (Afran et al., 2014). Approximately one third of pregnant women who received ART for the prevention of mother-to-child transmission (PMTCT) globally are from South Africa (Dwyer-Lindgren et al., 2019; World Health Organization, 2018). The population of HEU infants in South Africa is approximately 3.5 million which is five times more than the year 2002, when PMTCT was introduced as part of routine antenatal care (UNAIDS, 2019). HEU infants are a growing population in South Africa and are at potential risk of morbidity and mortality due to in-utero exposures related to maternal HIV (Springer , et al., 2012). In addition, there is some evidence to suggest that HEU infants may have poorer developmental outcomes(Le Roux et al.,2016; Springer et al., 2019).

Alongside the large population of HEU infants, the highest incidences of unplanned pregnancies occur in Sub-Saharan Africa, with a particularly high incidence occurring among women who are newly initiated on ART (Adeniyi et al., 2018; Feyissa et al., 2019). Women living with HIV (WLHIV) have increasingly become a topic of academic research globally, with South African WLHIV being more likely to experience an unplanned pregnancy compared to HIV negative women (Brittain et al., 2019; Iyun et al., 2018).

Studies have extensively analysed the effects of biomedical and environmental factors on the health outcomes of mothers as well as their HIV unexposed and uninfected (HUU), and HIV exposed and infected (HEI) infants (Grantham-McGregor et al., 2007; Sherr et al. 2014). However, there is a paucity of research examining the association between early child development and maternal psychosocial factors during pregnancy, including pregnancy intentions. Research analysis in the growing and vulnerable population of HEU infants is key for prevention strategies for unplanned pregnancy amongst WLHIV and poor development outcomes of HEU infants (Joyce, et al., 2000).

This research explored data from pairs of WLHIV and their HEU infants in Cape Town for the association between the intentions of pregnancy and early infant development among infants aged 36-60 months.

Methods

Study design

The data used in this study are from the "Long-term Adherence and Care Engagement" (LACE) study (May 2017-April 2018). The LACE study consisted of a single follow-up visit after the "Maternal-Child Health Antiretroviral Therapy" (MCH-ART) study (completed in 2016). The MCH-ART study enrolled WLHIV who were initiating ART during pregnancy and followed them through delivery. Women who then opted to breastfeed were randomly allocated to postpartum models of ART care and were followed through 12-18 months postpartum. The LACE study then aimed to assess longer-term outcomes among these women and their children, including the major biological, behavioural and health service determinants of these outcomes.

Both studies were conducted at the Gugulethu Midwife Obstetric Unit in Cape Town, South Africa.

Participants

The MCH-ART study enrolled pregnant women living with HIV who were >18 years of age and eligible to initiate ART. For the LACE study, mother-infant pairs who had participated in the MCH-ART study were invited to participate in a single follow up study visit between 36-60 months postpartum.

Mothers had previously consented to future contact for related research studies as part of MCH-ART. Informed consent was obtained from all mothers who attended the LACE study visit. The MCH-ART and LACE studies were reviewed and approved by the Columbia University Medical Center Institutional Review Board (CUMC-IRB) and the University Of Cape Town Faculty Of Health Sciences Human Research Ethics Committee (UCT-HREC).

The current analysis was also approved by the University Of Cape Town Faculty Of Health Sciences Human Research Ethics Committee (UCT-HREC). This was for the purposes of exploratory data analysis of data from the LACE study.

Measures

For the MCH-ART and LACE studies, trained research interviewers administered questionnaires in isiXhosa or English. All measures were validated for the South African context for use in the study.

To measure the pregnancy intention of the women, The London Measure of Unplanned Pregnancy (LMUP) questionnaire was administered at enrolment into the MCH-ART study. The tool assessed the retrospective circumstances of the most recent pregnancy and the family planning methods of women prior to the pregnancy (Barrett et al., 2004; Hall et al., 2017). The questionnaire is made up of six questions relating to timing of pregnancy, contraceptive use, the desire of the women and of the partner and planning(Barrett et al., 2004). Each question is scored between 0 and 2 and is totalled for a final score of 0-12. Scores can be categorized as: 0–3 (unplanned/unintended), 4–9 (ambivalent); and 10–12 (planned/intended)(Barrett et al., 2004; J. Hall et al., 2017).

For early infant development, The Ages and Stages (ASQ) standardized developmental screening tool for children under 5.5 years of age was administered among mother-infant pairs at the LACE study visit. The ASQ was previously standardised for use in clinical studies in Southern Africa(Hsiao et al., 2017) .The ASQ-3 assessed overall development across 5 domains; *Communication, Gross motor, Fine motor, Problem-solving, and Personal-social skills*.

The ASQ: SE-2 assessed *social-emotional* development of the infants. Both the ASQ-3 and ASQ: SE-2 were administered to each mother-infant pair, with the appropriate component of each selected based on the infant's age. The tool was designed to be used by parents or lay health professionals (Jane Squires et al., 1997). Each questionnaire had a standardized scoring sheet, with responses being "Always/Often", "Sometimes", or "Rarely/Never". Each response can take up a score value of either '0', '5' or '10'depending on the question. Cut-off scores vary per infant age and domain. For the ASQ-3, higher scores indicate a lower risk of delay and hence better development, whilst below the cut-off score, development is high risk for delay and hence poorer development. The high-risk score range has two possible outcomes for guidance: 'Monitor' or 'Refer'. For the ASQ: SE-2, lower scores indicate a lower risk of delay and hence better development, whilst above the cut-off score, development is considered poor and hence high-risk. The high-risk score range also has two possible outcomes for guidance:

'Monitor' or 'Refer'. For this analysis, scoring followed standardized guidelines and cut-off scores for developmental delay.

For maternal and infant socio-demographic characteristics, an additional questionnaire was administered to collect data. The Socio-demographic characteristics assessed for the women included: Age, socio-economic status (SES), education, marital status, and poverty. Clinical characteristics assessed included: Nulliparous (never been pregnant), gestational age at enrolment and if they were newly diagnosed with HIV during the pregnancy. For infants, demographic characteristics included gestational age, gender and preterm delivery.

Data analysis

Data was analysed using STATA v15.0 (Stata Corporation, College Station, Texas, USA).

Baseline socio-demographic and clinical characteristics were described using medians and inter-quartile ranges for continuous variables, and frequencies and percentages were used to describe categorical data. Socio-demographic and clinical characteristics were compared across categories of pregnancy intention using Chi-squared (X^2) and Kruskal Wallis tests.

Outcomes were modelled on a continuous scale based on the LMUP scores and the ASQ scores. Bivariate Linear Regression analysis was carried out on covariates of predictors on the response variable (Infant development). Multivariate Linear regression was performed to determine the possible associations between the intentions of pregnancy based on total LMUP scores on early child development ASQ 2& 3 scores. Confounders were selected *a priori*, included mother's age, SES, infant's gender, and adjustments were made for additional predictors, which include relationship status, Nulliparous, and gestational age at enrolment in the final multivariate linear regression model. *Beta* Coefficients and 95% confidence intervals are reported, along with their corresponding *P values*.

Results

Socio-demographic and clinical Characteristics

Of the initial 353 women enrolled into the LACE study, a total of 103 women and infants were excluded from this analysis on the bases that, 87 did not complete the ASQ, nine completed an incorrect ASQ for the infant's age, two infants had severe diagnosed developmental delay, and five women did not complete the LMUP questionnaire. As such, a sample **n=250** women remained and were included in the analysis.

Compared to women and infants who were included in the analysis, those who were excluded did not differ significantly according to any baseline characteristic (*Table I*)

Table 1: Comparison of socio-demographic and clinical characteristics of the women and infants who were included in the study analysis vs those who were excluded from the study analysis.

Variable	Included Total, n (%)	Excluded Total, n (%)	*P value*
Mothers	**250**	**103**	
Age years, Median [IQR]	28.3 [24.8 – 32.8]	27.6 [24.3 – 31.0]	0.118
Less than secondary education	189 (76)	78 (76)	0.980
Unemployed	153 (61)	59 (57)	0.484
Lowest SES	62 (25)	32 (31)	0.413
Married/or cohabiting	96 (38)	40 (39)	0.939
Nulliparous	47 (19)	12 (12)	0.102
Newly diagnosed (HIV)	140 (56)	54 (52)	0.540
Gestational age at enrolment (weeks), Median [IQR]	21 [16 - 26]	21 [14 - 26]	0.455
Infant	**250**	**103**	
Age(months), Median [IQR)]	44.1 [41.6 – 46.6]	43.8 [44.4 – 46.2]	0.487
Female	127 (51)	58 (56)	0.346
Preterm delivery	33 (13)	12 (12)	0.692

The median maternal age for women included in the analysis was 28.3 years (*Table 1*). Responses for further characteristics showed that 76% of the women had attained less than secondary school level education, 61% responded as unemployed, whilst 25% were from the lowest socio-economic status. As for marital status, 38% were married and/or cohabiting at the time of the pregnancy. Clinical characteristics showed that 56% of the women were newly diagnosed with HIV during the current pregnancy, whilst the current pregnancy was a first pregnancy (nulliparous) for 19% of the women.

Intention of pregnancy

Socio-demographic and clinical characteristics were described by subgroups of pregnancy intention (Unplanned, Ambivalent and Planned) (*Table 2*). Overall, 58% of women reported unplanned pregnancies, whilst 21% of pregnancies were categorised as planned and 21% as ambivalent.

Median gestational age (weeks) of pregnancy among women at the time of enrolment was 21 weeks overall for this sample, with women reporting that their pregnancies were unplanned being more likely to enrol for care at a later gestation (median of 22 weeks versus 21 weeks among those with planned pregnancies and 19 weeks among those reporting ambivalence; P=0.009). Planned pregnancies were more likely to occur among women who were married and/or cohabiting at the time of the pregnancy compared to those who were neither married nor cohabiting (P>0.001).

There was, however, no significant associations observed between pregnancy intention and the remaining baseline characteristics (P>0.05) as denoted in Table 2.

Table 2: Baseline socio-demographic and clinical characteristics of the women and their infants, stratified by intention of pregnancy category

Variable	**Total, n (%)**	**Unplanned, n (%)**	**Ambivalent, n (%)**	**Planned, n (%)**	***P value***
Mothers	**250**	**145 (58)**	**53 (21)**	**52 (21)**	
Age years, Median [IQR]	28.3 [24.8 – 32.8]	28.2 [24.7 – 33.0]	27.1 [25.5 - 31.4]	30.6 [25.2 – 33.2]	0.214
Less than secondary	189 (76)	112 (77)	41 (77)	36 (69)	0.487
Unemployed	153 (61)	85 (59)	33 (62)	38 (67)	0.537
Lowest SES	62 (25)	37 (26)	11 (21)	14 (27)	0.855
Married/or cohabiting	96 (38)	39 (27)	18 (34)	39 (75)	**<0.001**
Nulliparous	47 (19)	27 (19)	9 (17)	11 (21)	0.858
Newly diagnosed (HIV)	140 (56)	83 (57)	26 (49)	31 (60)	0.496
Gestational age at enrolment (weeks), Median [IQR]	21 [16 - 26]	22 [17 - 29]	19 [14 - 22]	21 [15 – 24]	**0.009**
Infant	**250**	**145 (58)**	**53 (21)**	**52 (21)**	
Age(months), Median [IQR)]	44.1 [41.6 – 46.6]	44.6 [42.3 – 46.8]	43.1 [40.5 – 45.2]	44.0 [42.8 – 46.8]	**0.05**
Female	127 (51)	76 (52)	20 (38)	31 (60)	0.068
Preterm delivery	33 (13)	18 (12)	9 (17)	6 (12)	0.650

Infant development

Eight percent of HEU infants scored below the threshold (ASQ-3) for gross motor skills, suggesting a delay in gross motor development (*Figure 1*). In addition, 19% of infants had evidence of delayed development for fine motor skills; 4% for communication; 15% for problem solving; and 7% for personal social development. For the socio-emotional domain (ASQ: SE-2), 2% of the infants scored above the threshold and hence had evidence of poorer development in this domain (*Figure 1*).

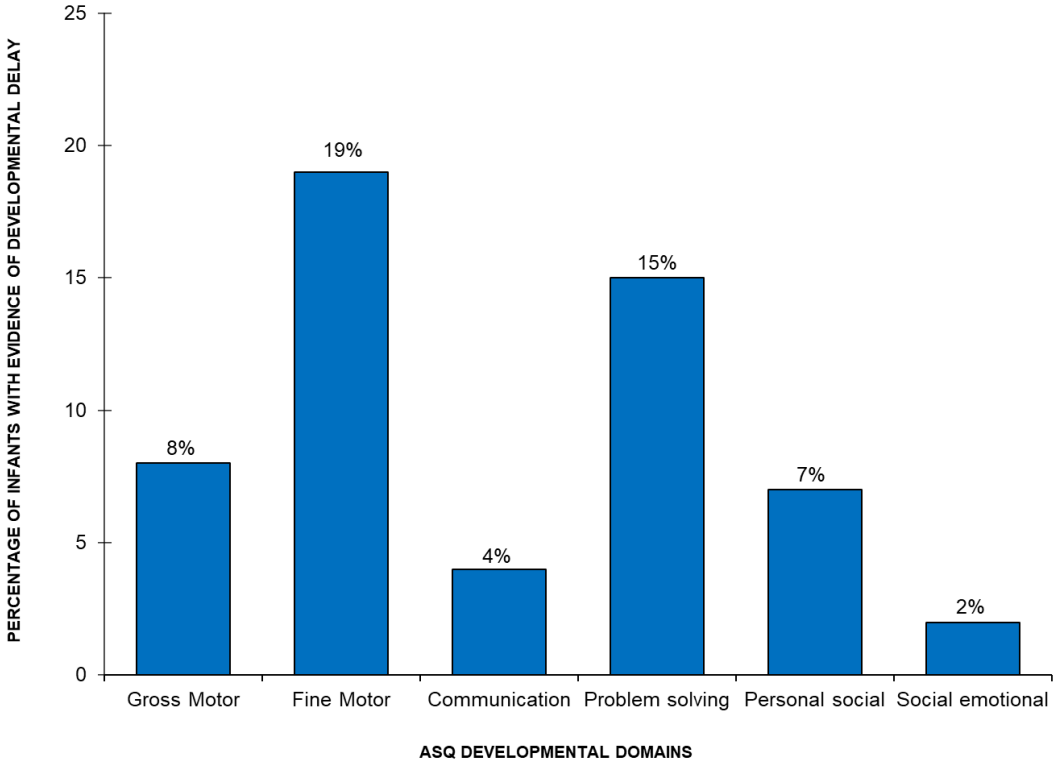

Figure 1: Percentages of HEU infants with evidence of developmental delays.

Effect of Intention of pregnancy on infant development

Figure 2 presents the proportion of infants with evidence of developmental delay in each domain by categories of pregnancy intention. Women whose pregnancies were planned or ambivalent had lower percentages of infants with evidence of developmental domains across the developmental domains, as compared to those with unplanned pregnancies (*Figure 2*).

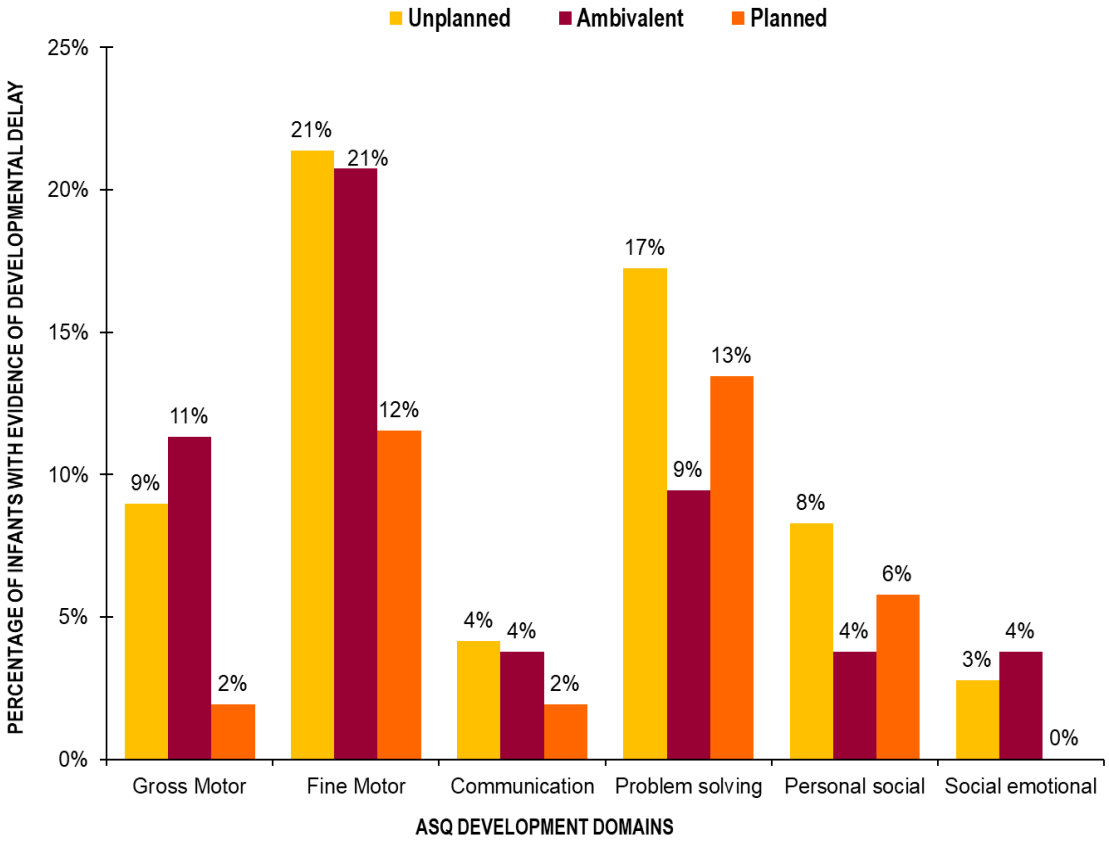

Figure 2: Percentage of infants with evidence of developmental delay by category of mother's pregnancy intention

Univariate Linear regression was performed to determine the effect of the LMUP scores and predictors on the ASQ scores for each child development domains (*Table 3*). No significant associations were observed between pregnancy intentions and early child development in any domain in univariate models or after adjustment for maternal demographic and clinical characteristics.

Table3: Linear Regression analysis for the prediction of Intention of pregnancy on Infants development (Adjusted and Unadjusted models)

Variable	Unadjusted coefficient [95% CI]	P-value	Adjusted coefficient [95% CI][a]	P-value
Communication [b]				
Intention of pregnancy [c]	-0.0045 [-0.269 - 0.260]	0.974	-0.0044 [-0.289 - 0.280]	0.976
Maternal age	-0.14 [-0.230 - 0.280]	0.103	-0.20 [-0.393 - 0.015]	**0.034**
Married	0.53 [-1.380 - 2.430]	0.587	1.09 [-1.010 - 3.210]	0.309
SES	-0.11 [-0.710 -0.500]	0.733	0.01 [-0.607 - 0 .627]	0.974
Nulliparous	-0.056 [-2.430 - 2.320]	0.963	-1.08 [-3.790 - 1.630]	0.434
Gestational age at enrolment	0.085 [-0.0350 - 0.210]	0.166	0.10 [-0.0222 - 0.223]	0.108
Infant gender	-1.45 [-3.290 - 0.399]	0.124	-1.47 [-3.320 - 0.380]	0.119
Gross motor [b]				
Intention of pregnancy [c]	-0.12 [-1.480 - 0.390]	0.375	0.17 [-0.118 - 0.455]	0.248
Maternal age	-0.098 [-0.270 - 0.070]	0.253	-0.089 [-0.279 - 0.101]	0.359
Married	0.45 [-1.500 - 2.400]	0.648	0.75 [-1.380 - 2.880]	0.489
SES	-0.11[-0.730 - 0.510]	0.721	-0.075 [-0.697 - 0.546]	0.812
Nulliparous	1.822 [-0.595 - 4.240]	0.139	1.48 [-1.260 - 4.210]	0.289
Gestational age at enrolment	0.18 [0.630 - 0.310]	**0.003**	0.21 [0.0830 - 0.330]	**0.001**
Infant gender	-1.36 [-3.250 - 0.527]	0.157	-1.46 [-3.310 - 0.404]	0.124
Fine motor [b]				
Intention of pregnancy [c]	0.19 [-0.250 - 0.630]	0.395	0.123 [-0.349 - 0.605]	0.609
Maternal age	-0.062 [-0.330 - 0.210]	0.653	-0.044 [-0.359 - 0.270]	0.782
Married	0.90 [-2.260 - 4 .0590]	0.574	0.95 [-2.570 - 4.480]	0.595
SES	0.38 [-0.620 - 1.380]	0.452	0.36 [-0.670 - 1.390]	0.486
Nulliparous	1.53 [-2.400 - 5.450]	0.445	1.34 [-3.180 - 5.870]	0.559
Gestational age at enrolment	-0.61 [-0.260 - 0.140]	0.549	-0.035[-0.240 - 0.170]	0.739
Infant gender	-3.07 [-6.120 - , -0.0207]	**0.048**	-3.09 [-6.170-, -0.0170]	**0.049**
Problem solving [b]				
Intention of pregnancy [c]	0.12 [-0.27-0.51]	0.554	-0.038 [-0.456- 0.380]	0.858
Maternal age	-0.056 [-0.30-0.19]	0.651	-0.050 [-0.327- 0.227]	0.721
Married	1.571 [-1.227-4.37]	0.270	1.88 [-1.23- 4.98]	0.235
SES	0.39 [-0.50-1.28]	0.384	0.37 [-0.54 - 1.28]	0.441
Nulliparous	1.19 [-2.30-4.68]	0.502	1.23 [-2.76 5.21]	0.451
Gestational age at enrolment	-0.17 [-0.34-0.011]	0.066	-0.15 [-0.328 0.032]	0.107
Infant gender	-2.91 [-5.62- -0.209]	**0.035**	-2.90 [-5.61- -0.19]	**0.036**
Personal Social [b]				
Intention of pregnancy [c]	0.054 [-0.22-0.32]	0.691	0.0026 [-0.283- 0.289]	0.986
Maternal age	-0.077 [-0.24-0.091]	0.368	-0.13 [-0.320 - 0.059]	0.177
Married	1.67 [-0.263-3.597]	0.09	2.22 [0.098- 4.35]	**0.04**
SES	-0.095 [-0.71-0.52]	0.761	0.018 [-0.602 0.638]	0.954
Nulliparous	0.52 [-1.893-2.938]	0.671	0.287 [-2.44- 3.01]	0.836
Gestational age at enrolment	0.11 [-0.15-0.23]	0.086	0.13 [0.0040- 0.250]	**0.043**
Infant gender	-2.46 [-4.32 -0.60]	**0.010**	-2.49 [-4.35 - -0.64]	**0.009**
Socio-emotional [b]				
Intention of pregnancy [c]	-0.32 [-1.05-0.40]	0.382	-0.117 [-0.885- 0.652]	0.776
Maternal age	-0.35 [-0.81-0.097]	0.123	-0.060 [-0.570-0.449]	0.816
Married	-8.10 [-13.26- (-)2.94]	**0.002**	-8.08 [-13.79 -2.37]	**0.006**
SES	-0.45 [-2.12-1.22]	0.598	-1.01 [-2.68-0 .656]	0.233
Nulliparous	4.24 [-2.285-1076]	0.202	2.51 [-4.81- 9.84]	0.500
Gestational age at enrolment	-0.35 [-0.68-0.017]	**0.039**	-0.42 [-0.749- -0.085]	**0.014**
Infant gender	3.96 [-1.13- 9.05]	0.127	3.90 [-1.09- 8.88]	0.125

[a] Models were adjusted for all covariates listed in the table

[b] Modelled on a continuous scale based on ASQ scores

[c] Modelled on a continuous scale based on LMUP scores

Discussion

This study explored the association between the intention of pregnancy of mothers living with HIV in Gugulethu, Cape Town and the development of their HEU infants. In this study, the majority of women reported that their pregnancy was unplanned. There was no significant association found between intention of pregnancy and infant development.

Prevention of unplanned pregnancy among WLHIV is pivotal for the prevention of vertical transmission and the fulfilment of global strategies for PMTCT (Feyissa et al., 2019). The high percentage of unplanned pregnancies in this study point out the importance for interventions aimed at the reduction of unplanned pregnancies amongst WLHIV (Feyissa et al., 2019). There is continued need for education for informed contraceptive care for the prevention of contraceptive failure, as well as adequate provisions for preconception health and care. All this being through the integrated and targeted ART, Antenatal and reproductive health services in South Africa (Berglund & Lindmark, 2016; Feyissa et al., 2019). This is to minimise adverse psychosocial outcomes related to unplanned pregnancy such as perinatal mental health issues such as stress and depression, which may attribute to negative feelings towards continued pregnancies (Stein et al., 2014).

The psychological effects of a HIV diagnoses are known to be initially devastating, especially with an unplanned pregnancy(Stinson & Myer, 2012); Brittain, et al, 2019). Previous findings from the MCH-ART study suggest that women whose pregnancies' were categorised as unplanned had the highest proportion of depressive symptoms (Brittain, et al, 2019). Depressive symptoms potentially attribute to difficulty in mothers engaging with their infant positively, which can result in minimal regulation of emotion and hence insecure attachment of infants to their mothers (Haffejee et al., 2017). Whilst socio-emotional development relies on the exposure to positive experiences, the healthy expression of emotion is essential in the early development of an infant's ability to regulate emotion which requires parental support (Logan et al., 2007; Nelson & O'Brien, 2012). Depressive symptoms resulting from an unplanned pregnancy therefore affect the behavioural and psychosocial responsiveness of women affected ,attributing to maternal distress during pregnancy and postpartum (Choi et al., 2019; Ameyaw et al.,2019). Although no association was observed between pregnancy intentions and infant development in the current study, future work should explore the impact of pregnancy intentions on parenting behaviours.

Squires & Bricker, (2015) provide guidelines as part of the ASQ with suggestions for potentially simple and cost effective interventions, which can be applied in resource-limited communities. These interventions address contact time for bonding interactions among infant-mother pairs and hence stimulate personal social and social emotional development. Examples of suggestions include singing to and with infants, identifying objects, storytelling or reading, holding infants for close contact, playing with the infant as well as expressions of affection and affirmations(Squires et al., 2015; Squires & Bricker, 2009).

Limitations of the study include recall bias from the retrospective LMUP questionnaire responses and ASQ questionnaire responses by the women subject to social desirability bias. The responses of the women at the time of the visit may have evolved post-conception due to a change of emotion towards the pregnancy, as well as maternal psychosocial and environmental factors. These may have resulted in underreporting and misclassification, potentially diluting the effect of pregnancy intention on early child development. Another limitation related to the ASQ includes self-reported response bias for infant development by mothers, based on potential differences in interpretations of questions. Whilst other limitations were related to the small sample size, for future suggestions a larger sample size will be ideal if this study is to be replicated. As the outcome of delayed development in this study was rare, a larger sample and robust models would be needed to investigate the effect of pregnancy intention on developmental delay in some domains.

In summation, this study found a high prevalence of unintended pregnancy, but no association was observed between pregnancy intentions and early child development. . The findings of this research accentuate the need for targeted strategies towards psychosocial issues, and educational interventions for WLHIV and, for informed fertility decisions. Furthermore, the need for exploration of interventions to encourage infant-parent attachment and interaction for development, as well as the impact of pregnancy intentions on parenting behaviours.

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Conflict of Interest

None

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PART D: APPENDICES

List of Appendices :

Appendix 1: HREC Approval letter for the proposed study

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

03 February 2020

HREC REF:858/2019

Dr K Brittain
Division of Epidemiology & Biostatistics
Entrance 5, Level 5 Office 5.47
Falmouth Building-FHS

Dear Dr Brittain

PROJECT TITLE: INVESTIGATING THE INTENTION OF PREGNANCY AMONG WOMEN LIVING WITH HIV AND ITS EFFECT ON THE EARLY DEVELOPMENT OF THEIR HIV EXPOSED INFANTS (SUB-STUDY 451/2012) (MASTER'S DEGREE - MISS CHIDO MOYO)

Thank you for your response letter dated 22 January 2020, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 28 February 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Miss Chido Moyo will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 858/2019sa

NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 2: Author instructions for Manuscript preparation

Maternal Child Health Journal
Instructions for Authors

Types of Papers

The Journal is interested in original research in the area of maternal and child health, both within the
US and from other countries. As this is primarily a journal devoted to population health, we are not
Interested in clinical case studies, in papers that are exclusively clinically focused, or in research that
Does not have an obvious public health focus. Research or practice-based articles from communities
Within the United States and from countries outside the US are welcome as long as they address
Issues of maternal and child health that will be of interest to more than a local audience.

Manuscripts of the following types are welcome:

Original Research reports (3500-word limit) results from an empirical research study, whether Quantitative or qualitative, on a focused topic, presented consistent with international guidelines for
Research reporting (see http://www.equator-network.org/reporting-guidelines). *Original Research* may
Also, take the format of a systematic review.

Reviews on specific, defined topics (3500 word limit) are welcome if they are systematic and
Reported in a standardized format. When justified, Reviews may exceed 35 references.

Reporting guidelines have been developed for different study designs. The Journal encourages authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, selecting, extracting, and synthesizing data; this is mandatory for systematic reviews. The Journal encourages authors to utilize the following standards:
For Observational Studies: STROBE http://strobe-statement.org/
For Qualitative Studies: COREQ http://www.equator-network.org/reportingguidelines/coreq/
For Systematic Reviews and Meta-Analyses: PRISMA http://prisma-statement.org/
For Randomized Trials: CONSORT http://www.consort-statement.org/
For Quality Improvement in Healthcare: SQUIRE http://squire-statement.org/
Other guidelines are available here:
http://www.nlm.nih.gov/services/research_report_guide.html
For additional information, see http://www.equator-network.org/reportingguidelines/
An example of an *Original Research* article is “New Evidence on Breastfeeding and Postpartum Depression: The Importance of Understanding Women’s Intentions” by Cristina Borra, Maria Iacovou, Almudena Sevilla which is available here:
http://link.springer.com/article/10.1007%2Fs10995-014-1591-z
Another example is “Complex Calculations: How Drug Use during Pregnancy Becomes a Barrier to Prenatal Care” by Sarah C. M. Roberts and Cheri Pies available here:
http://link.springer.com/article/10.1007/s10995-010-0594-7

From the Field articles (2500 word limit) report novel programs, policies, or interventions of interest to
a general maternal and child health audience, and may reflect evaluations, assessments, or other Systematic description. *From the Field* articles may share a local experience that has potential applicability to other communities. Authors are encouraged to describe the context clearly to ensure
readers in other areas understand what is important and what has changed. Specific types of *From the*
Field articles might include:
Field or practice-based articles (2500 word limit) that describe new models, demonstrate the effectiveness of new or modified interventions, discuss the development or impact of new policies, or evaluate large or small-scale programs.
Methodological Notes (2500 word limit) report upon focused, specific methodological issues of interest to maternal and child health researchers and practitioners, and can address qualitative, quantitative, policy, or other research modalities. Methodological notes may describe innovations in data gathering, measurement, study design, assessment and evaluation.
Professional Development manuscripts (2500 word limit) present systematic descriptions and analyses of aspects of maternal and child health career paths, skills, leadership, and training.
Policy Briefs (2500 word limit) describe the development and/or implementation of particular policies at any level of administration that may relate to maternal and child health.
Brief Reports (2500 word limit) are short analyses of specific topics, usually reflecting the results of empirical research of general interest.
Graduate Education pieces (2500 word limit) describe novel educational curricula development, educational interventions, or evaluations, broadly useful to maternal and child health and related fields.
Historical Notes (2500 word limit) present historical accounting and analysis of key developments in maternal and child health and may reflect aspects of clinical care, maternal and child health programming, education, or administration, or more general public health developments in the field.
An example of a *From the Field* article is “Routine Prenatal HIV Testing: Women’s Concerns and Their Strategies for Addressing Concerns” by Pamela Rothpletz-Puglia, Deborah Storm, Carolyn Burr, and Deanne Samuels and is available here:
http://link.springer.com/article/10.1007/s10995-011-0754-4.
Commentary or *Letters to the Editor* (2500 word limit) reflect a systematically presented opinion around a
particular issue of maternal and child health interest, often promoting new ideas or directions. For
specific guidance on how to prepare these, please see
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2647072/.
An example of a *Commentary* is “Racial and Ethnic Disparities in Birth Outcomes: A Life-Course Perspective” by Michael C. Lu and Neal Halfon and is available here:
http://link.springer.com/article/10.1023/A%3A1022537516969

Article Length

As a general rule, the more concise the presentation, the better. Large-scale program evaluations,
complex practice-based interventions, and some quantitative research may be allowed a few additional pages, if there is strong justification provided in a separate note to the editor. There is no

need to repeat in text what is presented in tables and figures, and there is no need to repeat information from one section of the narrative to another.

 Original Research **articles, which include** ***Review*** **articles, should be limited to 3500 words with**
no more than 35 references.

 From the Field and *Commentary* or *Letters to the Editor* should be limited to 2500 words with no
more than 25 references.

Manuscript Submission

Submission is a representation that the manuscript has not been published previously and is not currently under consideration for publication elsewhere. A statement transferring copyright from the
authors (or their employers, if they hold the copyright) to Springer will be required before the manuscript can be accepted for publication. The Editor will supply the necessary forms for this transfer. Such a written transfer of copyright, which previously was assumed to be implicit in the act
of submitting a manuscript, is necessary under the U.S. Copyright Law in order for the publisher to
carry through the dissemination of research results and reviews as widely and effectively as possible.

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Online Submission

Authors should submit their manuscripts online. Electronic submission substantially reduces the
editorial processing and reviewing times and shortens overall publication times. Please follow the
hyperlink “Submit online” on the right and upload all of your manuscript files following the instructions given on the screen.

Manuscripts should be submitted through the Editorial Manager Website for Maternal and Child
Health Journal at: http://www.editorialmanager.com/maci/

APA Style

APA Publication Manual standards must be followed. Please visit http://www.apastyle.org/ for the
guidelines.

Suggested Reviewers

Authors are asked to submit the names, current email addresses, and other contact information for
three (3) suggested reviewers for their article. These potential reviewers should not be members of
the authors’ departments or institutions, must not have participated in writing, editing, or reviewing
the submission, and should be qualified to address the topic of the article. The editors of the Journal

reserve the right to invite the suggested reviewers or other reviewers.

Integrity of Research and Reporting

Ethical standards

Manuscripts submitted for publication must contain a statement to the effect that all human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

It should also be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted.

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Authors must indicate whether or not they have a financial relationship with the organization that sponsored the research. This note should be added in a separate section before the reference list.

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Formatting Requirements

Order of Manuscript Pages

 Title Page with all Author Contact Information and the corresponding author e-mail information.
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 Tables, figures, footnotes, and legends should appear as separate sheets appended to the end of the manuscript.
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The title page should include:

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Abstract

A structured abstract of up to 250 words is to be provided. The abstract should provide the context
or background for the study and should state the study's purpose, basic procedures (selection of
study participants, settings, measurements, analytical methods), main findings (giving specific effect
sizes and their statistical and clinical significance, if possible), and principal conclusions. It should
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not overinterpret findings.
Because abstracts are the only substantive portion of the article indexed in many electronic databases,
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 For *Original Research* articles using the headings: Objectives, Methods, Results, and Conclusions for Practice.
 For *From the Field* articles use the headings: Purpose, Description, Assessment, and Conclusion.
 Another acceptable format for all article types is: Introduction, Methods, Results, and Discussion.

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Directly after the Abstract, the author should include a short paragraph (100 words or less) titled
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For example, the following paragraphs were included in "The educational gradient in coronary heart
disease: the association with cognition in a cohort of 57,279 male conscripts" by Inger Ariansen,
Laust Mortensen, Jannicke Igland, Grethe S Tell, Kristian Tambs, Sidsel Graff-Iversen, Bjørn Heine
Strand, and Øyvind Næss in *J Epidemiol Community Health* available here:
http://jech.bmj.com/content/early/2014/11/13/jech-2014-204597.full.pdf+html
"What is already known on this subject?
The socioeconomic gradient in coronary heart disease may not be fully explained by social differences in cardiovascular risk factors. Cognitive ability has been proposed to impact this gradient independently of cardiovascular risk factors.
"What this study adds?
Adjustment for established cardiovascular disease risk factors substantially attenuated the educational gradient in coronary heart disease. Although the remaining unexplained gradient was not further attenuated by cognitive ability, cognitive ability alone moderately attenuated the educational gradient. This suggests that cognitive ability may be linked to coronary heart disease through risk factors."

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See the APA Publication Manual (1994) pp. 292 298.

Sections of the Text

Introduction, Objectives, Purpose

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

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Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations.

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Emphasize the new and important aspects of the study and the conclusions that follow from them in the context of the totality of the best available evidence. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section. For experimental studies, it is useful to begin the discussion by briefly summarizing the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the
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 Book
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Abou-Allaban, Y., Dell, M. L., Greenberg, W., Lomax, J., Peteet, J., Torres, M., & Cowell, V. (2006). Religious/spiritual commitments and psychiatric practice. Resource document. American Psychiatric Association. http://www.psych.org/edu/other_res/lib_archives/archives/200604.pdf. Accessed 25 June 2007.

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